Proposed Registration Decision PRD2010-09

Lactobacillus casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis ssp. lactis* strain LL64/CSL, *Lactococcus lactis ssp. lactis* strain LL102/CSL, *Lactococcus lactis ssp. cremoris* strain M11/CSL

(publié aussi en français)

4 May 2010

This document is published by the Health Canada Pest Management Regulatory Agency. For further information, please contact:

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Canada

HC Pub: 100211

ISBN: 978-1-100-14941-7 978-1-100-15789-4
Catalogue number: H113-9/2010-9E H113-9/2010-9E-PDF

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Overview

Proposed Registration Decision for *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strains LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL

Health Canada's Pest Management Regulatory Agency (PMRA), under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of *Lactobacillus casei* Technical, *Lactobacillus rhamnosus* Technical, *Lactococcus lactis* ssp. *lactis* Technical and *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate and the end-use product Organo-Sol, containing the microbial pest control agents *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, for the partial suppression of clovers, black medick, bird's-foot trefoil, and wood sorrel in established lawns.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

This Overview describes the key points of the evaluation, while the Science Evaluation provides detailed technical information on the human health, environmental and value assessments of Lactobacillus casei Technical, Lactobacillus rhamnosus Technical, Lactococcus lactis ssp. lactis Technical and Lactococcus lactis ssp. cremoris Technical, DOM Manufacturing Concentrate and Organo-Sol.

What Does Health Canada Consider When Making a Registration Decision?

The key objective of the *Pest Control Products Act* is to prevent unacceptable risks to people and the environment from the use of pest control products. Health or environmental risk is considered acceptable[1] if there is reasonable certainty that no harm to human health, future generations or the environment will result from use or exposure to the product under its proposed conditions of registration. The Act also requires that products have value[2] when used according to the label directions. Conditions of registration may include special precautionary measures on the product label to further reduce risk.

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1 "Acceptable risks" as defined by subsection 2(2) of the *Pest Control Products Act.*

2 "Value" as defined by subsection 2(1) of the *Pest Control Products Act*: "the product's actual or potential contribution to pest management, taking into account its conditions or proposed conditions of registration, and includes the product's (*a*) efficacy; (*b*) effect on host organisms in connection with which it is intended to be used; and (*c*) health, safety and environmental benefits and social and economic impact."

To reach its decisions, the PMRA applies modern, rigorous risk-assessment methods and policies. These methods consider the unique characteristics of sensitive subpopulations in humans (e.g. children) as well as organisms in the environment (e.g. those most sensitive to environmental contaminants). These methods and policies also consider the nature of the effects observed and the uncertainties when predicting the impact of pesticides. For more information on how the PMRA regulates pesticides, the assessment process and risk-reduction programs, please visit the Pesticide and Pest Management portion of the Health Canada's website at healthcanada.gc.ca/pmra.

Before making a final registration decision on *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, the PMRA will consider all comments received from the public in response to this consultation document[3]. The PMRA will then publish a Registration Decision[4] on *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, which will include the decision, the reasons for it, a summary of comments received on the proposed final registration decision and the PMRA's response to these comments.

For more details on the information presented in this Overview, please refer to the Science Evaluation of this consultation document.

What Is *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL?

Lactobacillus casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL are lactic acid bacteria that produce the fermentation products citric acid and lactic acid. Due to the presence of citric acid and lactic acid in the end-use product Organo-Sol, it has a low pH (~3.5) that allows for penetration of plant cells causing tissue necrosis and suppression of plant growth. Plant species most susceptible to Organo-Sol are those with a thin leaf cuticle. Organo-Sol is a commercial herbicide used for the partial suppression of clovers, black medick, bird's-foot trefoil, and wood sorrel in established lawns.

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3 "Consultation statement" as required by subsection 28(2) of the *Pest Control Products Act*.

4 "Decision statement" as required by subsection 28(5) of the *Pest Control Products Act*.

Health Considerations

Can Approved Uses of *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 and Their Fermentation Products, Citric Acid and Lactic Acid, Affect Human Health?

> ***Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 and their fermentation products, citric acid and lactic acid, are unlikely to affect your health when Organo-Sol is used according to the label directions.**

Exposure to *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 and their fermentation products, citric acid and lactic acid, may occur during handling of Organo-Sol.

When assessing the health risks associated with microbial active ingredients, several key factors are considered: a microorganism's biological properties (e.g., production of toxic byproducts), reports of any adverse incidents, potential to cause disease or toxicity as determined in toxicological studies and the level to which people may be exposed relative to exposures already encountered in nature to other isolates of this microorganism.

For biochemical actives, the levels where no health effects occur and the levels to which people may be exposed are considered. The dose levels used to assess risks are established to protect the most sensitive human population (e.g., children and nursing mothers). Only uses for which the exposure is well below levels that cause no effects in animal testing are considered acceptable for registration.

The lactic acid bacteria used in the manufacture of Organo-Sol and their organic acids are already occurring in the food chain for human consumption at similar levels to those found in Organo-Sol and there have been relatively few reports of infection or adverse effects despite their ubiquity.

The fermentation products, citric acid and lactic acid, are of low acute toxicity by the oral route. Lactic acid is of low acute toxicity via the dermal route while both lactic and citric acid are slightly irritating to the skin. Eye irritation studies indicated that, at the concentrations found in Organo-Sol, lactic acid and citric acid are capable of producing moderate to severe injury to the eye, particularly with repeated or prolonged exposure. Appropriate label statements and requirements for basic personal protective equipment will minimize exposure.

Residues in Water and Food

Dietary risks from food and water are not of concern.

As part of the assessment process prior to the registration of a pesticide, the PMRA must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit under the Pest Control Products Act for the purposes of the adulteration provision of the Food and Drugs Act. The PMRA sets science-based maximum residue limits to ensure the food Canadians eat is safe.

As there are no direct applications to food and no significant adverse effects were reported in Tier I acute toxicity/pathogenicity studies, the establishment of maximum residue limits are not required for *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, *Lactobacillus casei* strain LPT-111 and their fermentation products, citric acid and lactic acid. In addition, the likelihood of residues of *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, *Lactobacillus casei* strain LPT-111, citric acid or lactic acid contaminating drinking water supplies is negligible. Consequently, dietary exposure and risk are minimal to non-existent.

Occupational Risks From Handling Organo-Sol

Occupational risks are not of concern when Organo-Sol is used according to label directions, which include protective measures.

Users of Organo-Sol can come into direct contact with *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, *Lactobacillus casei* strain LPT-111, citric acid or lactic acid primarily via the skin or eyes. As a standard requirement intended to minimize exposure, the label specifies that users of Organo-Sol must wear water-proof gloves, long-sleeved shirts, long pants, shoes and socks and eye-goggles. Users are also directed to avoid inhaling the product and its mists.

As the end-use product may contain the allergen, unmodified milk protein (whey), the Organo-Sol label restricts entry and re-entry into treated areas until the spray is dried.

Environmental Considerations

What Happens When Organo-Sol Is Introduced Into the Environment?

Environmental risks are not of concern.

Lactic acid bacteria are considered widespread in nature and can be recovered from water, soil, manure, sewage, and silage as well as from a variety of plant material such as fruit, vegetables, grass, and clover. Lactic acid bacteria are also part of the commensal microflora of humans and animals as part of the gastrointestinal tract, oral cavity, and vagina. Published literature indicates that although lactic acid bacteria can survive outside of the dairy environment they are unlikely to thrive. As well, the number of lactic acid bacteria contained in Organo-Sol is relatively low. Since the use of Organo-Sol is not likely to result in an increase of the number of lactic acid bacteria in the environment, the risk to terrestrial and aquatic non-target organisms from lactic acid bacteria is negligible.

Citric acid and lactic acid readily undergo biotransformation in terrestrial and aquatic environments. Given the ubiquitous nature of citric acid and lactic acid in animals, plants, edible food commodities and industrial chemicals, the proposed uses of Organo-Sol on lawns is not expected to result in a considerable increase in exposure to non-target terrestrial and aquatic organisms. Furthermore, reports in published literature of cases of adverse effects, as well as published toxicological endpoints, do not suggest that exposure of non-target terrestrial and aquatic organisms to the levels of citric acid and lactic acid in Organo-Sol will pose a concern with respect to toxicity. Based on the available data, citric acid and lactic acid are expected to pose negligible risk to terrestrial and aquatic organisms under the conditions of use.

Value Considerations

What Is the Value of Organo-Sol?

Acids in Organo-Sol produced by living lactic acid bacteria cause cell necrosis and suppression of plant growth after penetrating into plant cells.

Application of Organo-Sol provides partial suppression of white clover, red clover, bird's-foot trefoil, black medick, and wood sorrel in established lawns. Based on the mode of action of Organo-Sol, development of herbicide resistance is unlikely. The availability of Organo-Sol contributes to an integrated and sustainable pest management program in turf.

Measures to Minimize Risk

Labels of registered pesticide products include specific instructions for use. Directions include risk-reduction measures to protect human and environmental health. These directions must be followed by law.

The key risk-reduction measures being proposed on the label of Organo-Sol to address the potential risks identified in this assessment are as follows.

Key Risk-Reduction Measures

Human Health

To minimize exposure to *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 and their fermentation products, citric acid and lactic acid, all applicators, mixer-loaders and handlers must wear water-proof gloves, long-sleeved shirts, long pants, shoes and socks and eye goggles. A label statement directing users to avoid inhaling the product and its mists is also included.

As the end-use product may contain the allergen, unmodified milk protein (whey), the Organo-Sol label restricts entry and re-entry into treated areas until the spray is dried.

Environment

As a general precaution, statements will be added to the label to prevent handlers from contaminating aquatic habitats and systems, and to prevent the accidental treatment of desirable plants with Organo-Sol.

Next Steps

Before making a final registration decision on *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111, the PMRA will consider all comments received from the public in response to this consultation document. The PMRA will accept written comments on this proposal up to 45 days from the date of publication of this document. Please forward all comments to Publications (contact information on the cover page of this document). The PMRA will then publish a Registration Decision, which will include its decision, the reasons for it, a summary of comments received on the proposed final decision and the Agency's response to these comments.

Other Information

When the PMRA makes its registration decision, it will publish a Registration Decision on *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 (based on the Science Evaluation of this consultation document). In addition, the test data referenced in this consultation document will be available for public inspection, upon application, in the PMRA's Reading Room (located in Ottawa).

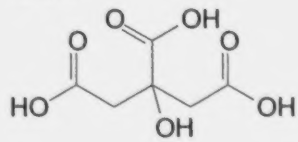
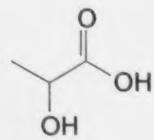
Science Evaluation

Lactobacillus casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL

1.0 The Active Ingredient, Its Properties and Uses

1.1 Identity of the Active Ingredient

Active microorganisms	*Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL				
Function	Produces citric acid and lactic acid during fermentation				
Taxonomic designation					
Kingdom	Prokaryotes				
Phylum	Firmicutes				
Class	Bacilli				
Order	Lactobacillales				
Family	Lactobacilliaceae		Streptococcaceae		
Genus	*Lactobacillus*		*Lactococcus*		
Species	*casei*	*rhamnosus*	*lactis*		
Sub-species			*lactis*		*cremoris*
Strain	LPT-111	LPT-21	LL64/CSL	LL102/CSL	M11/CSL
Patent Status information	No patents are held by the applicant in Canada.				
Minimum purity of active (colony forming units [CFU]/g)	1.5×10^9	1.5×10^9	5.0×10^9	5.0×10^9	1.0×10^{10}
Identity of relevant impurities of toxicological, environmental and/or significance.	The TGAIs do not contain any impurities or micro contaminants known to be Toxic Substances Management Policy Track 1 substances. The product must meet microbiological contaminants release standards. *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL do not produce any known toxins or any other known toxic metabolites.				
Active biochemicals	Citric acid		Lactic acid		

Function	Herbicide	Herbicide
International Union of Pure and Applied Chemistry (IUPAC) name	2-hydroxypropane-1,2,3-tricarboxylic acid	2-hydroxypropanoic acid
CAS number	77-92-9	50-21-5
Molecular weight	192.12	90.08
Molecular formula	$C_6H_8O_7$	$C_3H_6O_3$
Structural formula		

1.2 Physical and Chemical Properties of the Active Ingredients and End-Use Product

Technical Grade Active Ingredient – *Lactobacillus rhamnosus* Technical

Physical state	Powder
Guarantee	*Lactobacillus rhamnosus* strain LPT-21: 1.5×10^9 CFU/g nominal

Technical Grade Active Ingredient – *Lactobacillus casei* Technical

Physical state	Powder
Guarantee	*Lactobacillus casei* strain LPT-111: 1.5×10^9 CFU/g nominal

Technical Grade Active Ingredient – *Lactococcus* lactis spp. *lactis* Technical

Physical state	Powder
Guarantee	*Lactococcus lactis* ssp. *lactis* strain LL64/CSL : 5.0×10^9 CFU/g nominal *Lactococcus lactis* ssp. *lactis* strain LL102/CSL : 5.0×10^9 CFU/g nominal

Technical Grade Active Ingredient – *Lactococcus* lactis spp. *cremoris* Technical

Physical state	Powder
Guarantee	*Lactococcus lactis* ssp. *cremoris* 1.0×10^{10} CFU/g nominal

Manufacturing Concentrate (MA) – DOM Manufacturing Concentrate

Physical state	Powder
Guarantee	*Lactococcus lactis* ssp. *lactis* strain LL64/CSL : 6.3×10^{10} CFU/g nominal *Lactococcus lactis* ssp. *lactis* strain LL102/CSL : 6.3×10^{10} CFU/g nominal *Lactococcus lactis* ssp. *cremoris* 1.3×10^{11} CFU/g nominal

End-Use – Organo-Sol

Physical state	Aqueous suspension
Guarantee	Citric acid ....19.71 g/L nominal (limits 15.77 – 23.65 g/L) Lactic acid ....17.69 g/L nominal (limits 14.16 – 21.22 g/L) (present as fermentation products of *Lactobacillus rhamnosus* Strain R-11, *Lactobacillus casei* Strain R215, *Lactococcus lactis* ssp. *cremoris* Strain M11/CSL, *Lactococcus lactis* ssp. *lactis* Strain LL102/CSL, and *Lactococcus lactis* ssp. *lactis* Strain LL64/CSL)
Colour	yellowish
Viscosity	6 centipoise
pH	3.4
Density	1.14 g/mL @20°C

1.3 Directions for Use

Organo-Sol is for partial suppression[5] of white clover, red clover, bird's-foot trefoil, black medick, and wood sorrel in established lawns.

Organo-Sol can be used as broadcast and spot treatments:

- For broadcast application, a mixture of Organo-Sol at 25% v/v of total solution plus surfactant (3% v/v) and water (72% v/v) is applied to turf infested with actively growing weeds. The maximum spray volume is 200 ml per m^2.

- For spot application, a mixture of Organo-Sol at 50% v/v of total solution plus surfactant (3% v/v) and water (47% v/v) is directly applied to individual weeds, such that spray coverage on weed foliage is uniform and complete, but not to the point of runoff.

When applied as a broadcast treatment, first use of Organo-Sol should be limited to a small area so as to confirm the tolerance of the grass species within the established lawns prior to adoption as a general practice.

[5] A claim of partial suppression is a level of pest management, which is less than suppression, as defined by commercial standards and expectations in the market. Usually, this claim is considered for non-conventional pesticides and in general, pest control ratings range between 30-65%.

Recommended surfactants are those containing paraffin mineral oil at 83% and a blend of surfactants at 17%, i.e. XA Oil Concentrate, Kornoil Concentrate, and Assist Oil Concentrate. The mix must be applied using a standard or industrial sprayer with flat-fan nozzles.

The first application of Organo-Sol can start in May or later. In order to provide a consistent level of weed control over the growing season, applications of Organo-Sol should be repeated every 2 weeks for a total of at least 5 times.

To maximize its effectiveness Organo-Sol should be used in conjunction with a sound turf maintenance program.

1.4 Mode of Action

Due to a variety of organic acids (i.e. citric acid and lactic acid) produced by the lactic acid bacteria (i.e. *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* spp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* spp. *cremoris* strain M11/CSL) in the formulation, Organo-Sol has a low pH (~3). The low pH appears to be the main contributor to the mode of action of Organo-Sol as a weed management tool. Weed species most susceptible to Organo-Sol are those that have a thin leaf cuticle, which allows the acids in Organo-Sol to penetrate into plant cells causing tissue necrosis and suppression of plant growth.

2.0 Methods of Analysis

2.1 Methods for Identification of the Microorganism

Identification of lactic acid bacteria to the species level can be accomplished using random amplified polymorphic DNA PCR (RAPD-PCR) techniques. The method uses species-specific PCR identification targeted to 16S rRNA genes. Although there was no data provided for identification of the five microbial pest control agents themselves, the RAPD-PCR method would be adequate to identify the microbial pest control agents to the species level as *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactococcus lactis* ssp. *lactis* and *Lactococcus lactis* ssp. *cremoris*. *Lactococcus lactis* ssp. *lactis* can be differentiated from *Lc. lactic* ssp. *cremoris* using biochemical tests.

There was no method submitted for strain-specific identification. The registrant will be required to address this deficiency.

2.2 Methods for Establishment of Purity of Seed Stock

Practices for ensuring the purity of the seed stock were adequately described in the summary of the method of manufacture and quality assurance program.

2.3 Methods for Formulation Analysis of the End-use Product

The method provided for the analysis of the fermentation products, citric and lactic acid, in the formulation of the end-use product has been validated and assessed to be acceptable for use as an enforcement analytical method.

2.4 Methods to Define the Content of the Microorganism in the Manufactured Material Used for the Production of Formulated Products

The presence of microbial pest control agents in the end-use product is shown to be less than 7.0×10^4 CFU/mL by using valid microbiological techniques to enumerate all aerobic bacteria present.

2.5 Methods to Determine and Quantify Residues (Viable or Non-viable) of the Active Microorganism and Relevant Metabolites

As part of the assessment process prior to the registration of a pesticide, the PMRA must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit under the Pest Control Products Act for the purposes of the adulteration provision of the Food and Drugs Act. The PMRA sets science-based maximum residue limits to ensure the food Canadians eat is safe.

Lactobacillus casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL do not produce any known toxic substances and are commonly used as fermentation agents in the production of food intended for human consumption. The mode of action of the microbial pest control agent is not toxin-mediated but is rather a function of the fermentation products, citric and lactic acid, which have a low pH causing tissue necrosis and suppression of plant growth

Based on the above information, the establishment of a maximum residue limit is not required for *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL. As a result, no methods to determine and quantify the residues of microbial pest control agents and relevant metabolites are required.

2.6 Methods for Determination of Relevant Impurities in the Manufactured Material

The quality control procedures used to limit contaminating microorganisms during manufacture of *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate, and Organo-Sol are acceptable. Any product that does not meet the applicant's specifications for microbial contamination is destroyed.

2.7 Methods to Show Absence of Any Human and Mammalian Pathogens

As noted in section 2.5, quality control procedures are used to limit microbial contamination in *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate, and Organo-Sol. These procedures include contamination checks to detect contaminating microbes.

Acceptable microbial contaminant analysis data were submitted for five batches of Organo-Sol.

3.0 Impact on Human and Animal Health

3.1 Toxicity and Infectivity Summary

Organo-Sol contains citric acid and lactic acid which are present as fermentation products of *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111.

The PMRA conducted a detailed review of waiver rationales submitted in support of the lactic acid bacteria used in the manufacture of Organo-Sol, lactic acid and citric acid in lieu of oral toxicity/pathogenicity, dermal toxicity, dermal irritation and eye irritation studies. The waiver requests were based on the rationale that the lactic acid bacteria and the organic acids are already occurring in the food chain for human consumption at similar levels to those found in Organo-Sol and that there have been relatively few reports of infection or adverse effects despite their ubiquity.

Although there have been reports of infection caused by lactic acid bacteria, most cases have only occurred in immunocompromised individuals or individuals with underlying conditions. Given the widespread use of lactic acid bacteria in food products, probiotics and, in the case of lactobacilli, their presence as commensal organisms, the incidence of adverse effects attributed to lactic acid bacteria is low. At the concentrations present in Organo-Sol, the lactic acid bacteria are not expected to pose a significant risk via the oral route of exposure. Literature searches failed to yield reports of dermal toxicity or irritation associated with the lactic acid bacteria used in the manufacture of Organo-Sol. Similarly eye irritation was not reported for the *Lactobacillus* species. One case of canaliculitis was associated with a mixed infection of *Eikenella corrodens* and *Lactococcus lactis* ssp. *cremoris*. *Eikenella corrodens* is part of the normal flora in the human oral cavity and has been reported in other cases of canaliculitis.

Both citric acid and lactic acid are commonly found in food and natural health products. Acute oral toxicity studies on lactic acid have yielded LD_{50} values ranging from 1810 mg/kg bw (guinea pigs) to 4857 mg/kg (mice) thereby classifying lactic acid as slightly acutely toxic to being of low acute toxicity. Similar testing on citric acid resulted in LD_{50} values of 3000-11700 mg/kg bw in rats and 5000-5040 mg/kg bw in mice thereby classifying citric acid as being of low acute toxicity via the oral route. Lactic acid was found to be of low acute toxicity via the dermal route with an LD_{50} of >2000 mg/kg bw in rabbits. At concentrations of up to 25%, lactic acid was found to cause slight irritation. Dermal toxicity data were not available for citric acid. At

concentrations of up to 30%, citric acid appeared to be slightly irritating to the skin. Dermal irritation due to lactic acid or citric acid is likely pH dependent. Eye irritation studies indicated that, at the concentrations found in Organo-Sol, lactic acid and citric acid are capable of producing moderate to severe injury to the eye, particularly with repeated or prolonged exposure.

Lactic acid was not found to be a dermal sensitizer. Although no hypersensitivity studies were available on the lactic acid bacteria used in the manufacture of Organo-Sol or citric acid, their levels in the technical and/or end-use products along with their extensive history of use in food production indicate that there is minimal risk of sensitization. The Organo-Sol end-use product, however, may contain unmodified milk protein which is considered an allergen. Therefore, the primary panel of the Organo-Sol label must include the statement "WARNING – CONTAINS THE ALLERGEN MILK (WHEY PROTEIN)".

3.2 Occupational / Bystander Exposure and Risk Assessment

3.2.1 Occupational

When handled according to the label instructions, the potential routes of handler exposure to the lactic acid bacteria used in the manufacture of Organo-Sol, citric acid and lactic acid are pulmonary, dermal and to some extent ocular.

The potential for dermal, eye and inhalation exposure for applicators, mixer/loaders, handlers and early-entry workers exists, with the primary source of exposure to workers being dermal. Since unbroken skin is a natural barrier to microbial invasion of the human body, dermal absorption could occur only if the skin were cut, if the microbe were a pathogen equipped with mechanisms for entry through or infection of the skin, or if metabolites were produced that could be dermally absorbed. These microbial pest control agents have not been identified as wound pathogens and there is no indication that they could penetrate intact skin of healthy individuals.

Dermal irritation has been noted for lactic acid and citric acid. Furthermore, the pH of Organo-Sol is likely to cause dermal, eye and, to a lesser extent, pulmonary irritation, particularly with repeated or prolonged exposure. Risk mitigation measures and label statements are required to protect populations that are likely to be primarily exposed to Organo-Sol. Hazard statements to be included on the principal display panel should mirror end-use products with a similar pH and similar degree of irritancy. The pH of Organo-Sol is expected to be severely irritating to the eyes and mildly irritating to the skin but is not considered corrosive. Dermal and ocular exposure to applicators, mixer-loaders, handlers and early-entry workers can be minimized if they wear water-proof gloves, long-sleeved shirts, long pants, shoes and socks and eye-goggles. A label statement directing users to avoid inhaling the product and its mists is also required.

As the end-use product may contain the allergen, unmodified milk protein, the Organo-Sol label must include the statement "DO NOT re-enter or allow entry into treated areas until the spray is dried".

3.2.2 Bystander

The label allows applications to public and residential lawns. Therefore, there is a potential for non-occupational exposure to adults, infants and children. Overall, however, the PMRA does not expect that bystander exposures will pose an undue risk on the basis of the low toxicity / pathogenicity profile for the lactic acid bacteria species, citric acid and lactic acid in Organo-Sol. As the end-use product contains the allergen, unmodified milk protein, the Organo-Sol label must include the statement "DO NOT re-enter or allow entry into treated areas until the spray is dried".

3.3 Dietary Exposure and Risk Assessment

3.3.1 Food

Organo-Sol is not proposed for use on food or feed crops and the label directs users to avoid spraying fruits and vegetables. Therefore, negligible to no risk is expected for the general population, including infants and children, or animals because there are no direct applications of Organo-Sol to food or feed crops. As a result, there is no concern for chronic risks posed by dietary exposure of the general population and sensitive subpopulations, such as infants and children.

3.3.2 Drinking Water

The likelihood that Organo-Sol could enter neighbouring aquatic environments as a result of run-off is negligible. No risks are expected from exposure via drinking water because exposure will be minimal and lactic acid bacteria used in the manufacture of Organo-Sol, citric acid and lactic acid are routinely used in food production. The Organo-Sol label will instruct users not to contaminate irrigation or drinking water supplies or aquatic habitats through equipment cleaning or waste disposal. Furthermore, municipal treatment of drinking water is expected to remove the transfer of residues to drinking water. Therefore, potential exposure to the lactic acid bacteria used in the manufacture of Organo-Sol, citric acid and lactic acid in surface and drinking water is negligible.

3.3.3 Acute and Chronic Dietary Risks for Sensitive Subpopulations

As the end-use product, Organo-Sol, is not intended for direct application to food crops, an acute reference dose (ARD) and an acceptable daily intake (ADI) for citric acid and lactic acid are not required.

Calculations of ARDs and ADIs are not usually possible for predicting acute and long term effects of microbial agents in the general population or to potentially sensitive subpopulations, particularly infants and children. The single (maximum hazard) dose approach to testing microbial pest control agents is sufficient for conducting a reasonable general assessment of risk if no significant adverse effects (i.e., no acute toxicity, infectivity or pathogenicity endpoints of concern) are noted in acute toxicity and infectivity tests. Based on all the available information and hazard data, the PMRA concludes that the microbial pest control agents are of low toxicity,

are not pathogenic or infective to mammals, and that infants and children are likely to be no more sensitive to the microbial pest control agents than the general population. Thus, there are no threshold effects of concern and, as a result, no need to require definitive (multiple dose) testing or apply uncertainty factors to account for intra- and interspecies variability. Further factoring of consumption patterns among infants and children, and special susceptibility in these subpopulations to the effects of the microbial pest control agents (the lactic acid bacteria used in the manufacture of Organo-Sol), from pre- or post-natal exposures, and cumulative effects on infants and children of the microbial pest control agents do not apply to these microbial pest control agents. As a result, the PMRA has not used a margin of exposure approach to assess the risks of these microbial pest control agents to human health.

3.4 Maximum Residue Limits

As part of the assessment process prior to the registration of a pesticide, the PMRA must determine whether the consumption of the maximum amount of residues, that are expected to remain on food products when a pesticide is used according to label directions, will not be a concern to human health. This maximum amount of residues expected is then legally established as a maximum residue limit under the Pest Control Products Act for the purposes of the adulteration provision of the Food and Drugs Act. The PMRA sets science-based maximum residue limits to ensure the food Canadians eat is safe.

As there are no direct applications to food, the establishment of a maximum residue limit is therefore not required for the lactic acid bacteria, citric acid or lactic acid in the Organo-Sol end-use product.

3.5 Aggregate Exposure

Based on the waiver rationales and other relevant information in the PMRA's files, there is reasonable certainty that no harm will result from aggregate exposure of residues of the lactic acid bacteria used in the manufacture of Organo-Sol, citric acid or lactic acid to the general Canadian population, including infants and children, when the pest control product is used as labelled. This includes all anticipated dietary (food and drinking water) exposures and all other non-occupational exposures (dermal and inhalation) for which there is reliable information. Although uses of Organo-Sol on public and residential lawns carry the potential for dermal and inhalation exposure to the general public, few adverse effects are expected as evidenced in the safe history of use of the lactic acid bacteria species in Organo-Sol, citric acid and lactic acid in food and natural health products.

3.6 Cumulative Effects

The PMRA has considered available information on the cumulative effects of residues and other substances that have a common mechanism of toxicity. These considerations included the cumulative effects on infants and children of such residues and other substances with a common mechanism of toxicity. Besides strains of the lactic acid bacteria found in food and natural health products, the PMRA is not aware of any other microorganisms, or other substances that share a common mechanism of toxicity with the active ingredients in the technical products. No

cumulative effects are anticipated if the residues of the lactic acid bacteria found in Organo-Sol interact with related strains of these microbial species.

4.0 Impact on the Environment

4.1 Fate and Behaviour in the Environment

Environmental fate testing is intended to demonstrate whether a microbial pest control agent is capable of surviving or replicating in the environment to which it is applied, and could provide an indication of which non-target organisms may be exposed to the microbial pest control agent as well as provide an indication of the extent of exposure. Environmental fate data (Tier II/III) are not normally required at Tier I, and are only triggered if significant toxicological effects in non-target organisms are noted in Tier I testing. Since toxicological effectes were not noted, no fate data are required to complete the environmental risk assessment of *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, and *Lactococcus lactis* ssp. *cremoris* Technical when used to produce the end-use product Organo-Sol.

4.2 Effects on Non-Target Species

4.2.1 Effects on Terrestrial Organisms

Requests to waive testing on non-target terrestrial organisms with lactic acid bacteria and lactic and citric acid were accepted based on the following information.

4.2.1.1 Effects on terrestrial organisms from lactic acid bacteria

A literature search was conducted to determine whether there have been cases of infection in animals, including birds, mammals, or insects from lactic acid bacteria in general, and from *Lactobacillus rhamnosus, Lactobacillus casei, Lactococcus lactis ssp. lactis and Lactococcus lactis ssp. cremoris*, specifically.

In birds, a single case of infection by *Lactococcus lactis* ssp. *lactis* was reported in waterfowl. The case consisted of a mass die-off (> 3000 birds; 20%) of waterfowl in Spain attributed to *Lactococcus lactis* ssp. *lactis*. Predominantly affected bird species included coots (*Fulica atra*; 26.9%), shovelers (*Anas clypeata*; 25.1%), and mallards (*Anas platyrrhunchos*; 13.8%). Affected birds showed general weakness, and approximately half of the birds had respiratory distress. At necropsy most animals had mild lung congestion but no other lesions at post-mortem examination. Isolates recovered from lungs, liver and spleen of affected animals (11 samples) all had identical biochemical profiles, confirming that the infection was produced by a single strain of *Lactococcus lactis* ssp. *lactis* as identified by Rapid ID 32Strep system. Identification was also confirmed by polymerase chain reaction and pulsed-field gel electrophoresis. Although the recovery of *Lactococcus lactis* ssp. *lactis* in pure culture from the clinical sample would suggest clinical significance of the isolate, no direct link between *Lactococcus lactis* ssp. *lactis* infection and this episode could be established. Other than this one report, there have been no other cases

of adverse effects in birds due to natural populations of *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactococcus lactis* ssp. *lactis*, or *Lactococcus lactis* ssp. *cremoris*.

Although lactic acid bacteria are usually non-pathogenic to mammals, the published literature did reveal a number of reports of serious infections from lactic acid bacteria in humans over the years. The cases involved bacteræmia, endocarditis and localized infections. Generally, lactobacilli are considered ubiquitous gram-positive anaerobic rods present in the normal bacterial flora of mammals (including humans) in the mouth, vagina and gastrointestinal tract of humans. There were no cases of adverse effects in mammals other than in humans.

The published literature revealed no reports of adverse effects from lactic acid bacteria to arthropods. In fact, *Lactococcus lactis* ssp. *lactis* has been recovered in low numbers from certain insect species such as from the hindgut of termites, and the midgut of the Brown House Moth, *Hofmannophila pseudospretella*.

For non-arthropod invertebrates, *Lactococcus lactis* ssp. *lactis* has been recovered in low numbers from earthworms (*Eisenia fetida*). Two published studies examined the effect of dairy sludge on earthworm populations. The first studied the feasibility of vermicomposting dairy biosolids. This study demonstrated that when the epigenic earthworm (*Eisinea andrei*) was added directly to dairy biosolids (dairy sludge), either alone or with cereal, straw or wood shavings (as bulking agents) the worms died within 48 hours. However, the adverse effects of the dairy biosolids were overcome when the substrates were placed over a layer of vermicomposted sheep manure prior to addition of the earthworms. Under these conditions, all earthworms migrated to the upper layer of substrate within two weeks and, compared to sheep manure alone, the dairy biosolids plus bulking agents were more effective in supporting earthworm growth and reproduction (e.g., 39–53% less organic carbon after 63 days of vermicomposting; lower heavy metal contents and electrical conductivities). These results suggest that while exposure to high levels of dairy sludge may be detrimental to worms, the use of Organo-Sol as a diluted solution by broadcast application (25% solution) or spot-treatments (50% solution) in established lawns is not expected to have a considerable impact on earthworm populations.

The second study investigated the practice of irrigating fields with dairy effluent, and its effects on earthworm populations. The site that was studied had been irrigated regularly with dairy factory effluent for 22 years. The effluent consists of cleaning material and by-products of milk processing which typically contain high levels of carbon, nitrogen, and phosphorus, acids (as indicated by the pH of <7), as well as high proportions of lactose (1473 ± 873 g/m^3), and therefore high levels of lactic acid bacteria. The study revealed certain differences in earthworm populations; while the non-irrigated site (control site) had an overall greater abundance of earthworms than the irrigated site (303 worms±51 verses 214 worms± 33; ~30% decrease), the mean individual biomass of earthworms was greater in irrigated pastures (0.85g verses 0.51g). Five species of earthworms were identified from each site. *Lumbris terrestris* and *Octolasion cyaneum* had statistically significant lower abundance and biomass under irrigated conditions while *Lumbris castaneus* had a statistically significant greater abundance and biomass under irrigated conditions. *Aporrectodea longa* showed a statistically significant 3-fold increase in biomass but showed no significant increase in abundance.

No adverse effects from lactic acid bacteria to terrestrial plants were reported in published literature.

The lactic acid bacteria in Organo-Sol are present at a combined level of ~7.0×10^4 CFU/g. The use of Organo-Sol will be limited to broadcast applications or spot-treatments on lawns, with no extended agricultural uses. Given the widespread but sporadic exposure to functionally equivalent strains of *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Lactococcus lactis* ssp. *lactis* and *Lactococcus lactis* ssp. *cremoris* in the environment and as commensal organisms in humans and animals, and on the lack of persistence of the lactic acid bacteria in non-dairy environments, the proposed use of Organo-Sol is not expected to result in a considerable increase in exposure of non-target terrestrial animals. Despite a few reports of adverse effects in birds and humans, *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Lactococcus lactis* are not considered particularly pathogenic to terrestrial animals given the ubiquitous nature of these lactic acid bacteria in the environment. Furthermore, the microbial pest control agents in Organo-Sol are dairy-industry isolates, and it is generally accepted that dairy-industry isolates are seldom the source of clinical infections which further supports their non-pathogenic nature. All raw materials in the end-use product, Organo-Sol, are food-grade ingredients commonly used in the food industry for the manufacturing of food for humans (i.e., fermentation of dairy by-products) and animals. Based on these considerations, exposure to the lactic acid bacteria from the use of Organo-Sol is not expected to result in an unacceptable risk to non-target terrestrial organisms.

4.2.1.2 Effects on terrestrial organisms from lactic acids and citric acid

The following information was considered with respect to the potential for adverse effects on terrestrial organisms from lactic acid and citric acid.

Lactic acid is naturally present in animals and humans in muscle cells when the oxygen supply is inadequate to support energy production, and is normally excreted in human urine. In ruminants, lactic acid is a normal intermediate of feed digestion. Higher plants also contain lactic acid. Lactic acid is naturally present in many edible food commodities such as apples and other fruits, fruit juices, tomato juice, soft drinks, beer and wine, bakery goods, cheeses, candy, and salad dressings. It is also formed by natural fermentation in sour dairy products, fermented fruits and vegetables, and sausages.

Lactic acid has many chemical applications in industry such as salts, plasticizers, adhesives, in pharmaceuticals, as a mordant in dyeing wool, in de-hairing/plumping/and decalcifying hides, and as a solvent. It is reasonable to expect that these industrial uses may result in the release of lactic acid into the environment through various waste streams. In pesticides specifically, lactic acid is classified on the United States Environmental Protection Agency's (U.S. EPA) *List of Inert Ingredients* as a List 4B, an inert ingredient for which there is sufficient information to conclude that its current use pattern in pesticide products will not adversely affect public health and the environment. In Canada, there are currently no pesticide products registered with lactic acid as the active ingredient.

Citric acid is a weak organic acid that is found naturally in soil and water, natural waters, and sewage treatment systems. It plays a key role in the citric acid cycle, the metabolic energy system that is active in all animals and higher plants. Citric acid is also naturally present at high levels in many edible food commodities, such as in citrus fruit (particularly lemons and limes), raspberries, tomatoes, and potatoes.

Citric acid is also widely used in the food industry, as an acidulant in beverages (e.g., fruit juices), in confectionary, in pharmaceutical syrups, and in processing cheese, as well as in the chemical manufacturing, as a foam inhibitor, as a sequestering agent mordant, as an anticoagulant, as a buffering agent, for pH adjustments, and as a water conditioning agent for laundry detergents, shampoos, cosmetics, and chemical cleaning products. It is reasonable to expect that these industrial uses may result in the release of citric acid into the environment through various waste streams.

The U.S. EPA Re-Evaluation Decision for Citric acid reports that, in the U.S., citric acid is an active ingredient in certain domestic and commercial pesticide products such as bathrooms cleaners, disinfectants, sanitizers, and fungicides for use in and on food processing equipment (including dairy processing equipment). These products contain citric acid in combination with other active ingredients. There have been no incidents of adverse effects reported for citric acid in the U.S. Citric acid is classified on the U.S. EPA's *List of Inert Ingredients* as a List 4A which represents the U.S. EPA Minimum Risk Inerts List of ingredients that are generally regarded to be of minimal toxicological concern, as well as substances commonly consumed as food.

In Canada, there are currently no pesticide products registered with citric acid as the active ingredient.

A literature search conducted to determine whether there have been cases of adverse effects in terrestrial organisms reported no cases in birds, mammals, or plants from either lactic acid or citric acid.

For insects, there was one report of effects in *Varroa destructor*, the parasitic mite of honeybees, in a contact toxicity study with citric acid. Briefly, mites of different ages collected from the bee brood were exposed to citric acid or oxalic acid for 4 hours by placing 1 $\pm$0.05 mg/cm^2 of either acid on the mites (at 32.5°C and 75% relative humidity). After the exposure period, the mites were transferred to a clean glass Petri dish and observed for 48 hours. Due to considerable variability among replicates, treatment of the data was difficult. The 24-hour median lethal density (median density to kill 50% of the mite population; LD_{50}) of citric acid for mites varied from 3.04–9.34 µg/cm^2 active substance, and the 48-hour LD_{50} was 2.14–3.56 µg/cm^2 active substance. These values are much higher than those for oxalic acid which reported a 24-hour LD_{50} of 0.68–1.9 µg/cm^2 active substance, and a 48-hour LD_{50} was 0.64–1.02 µg/cm^2 active substance. While this study demonstrates that citric acid may display some degree of toxicity to the parasitic mite, the effects were observed after extended exposure (4 hours) to relatively high concentrations of citric acid. Neither of these exposure scenarios are likely to occur in nature, nor from the use of Organo-Sol given that citric acid demonstrates considerable biotransformation in the environment.

As discussed in Section 4.2.1.1, published literature also revealed two reports with respect to effect of dairy sludge on earthworm populations. One studied the feasibility of vermicomposting dairy biosolids, suggesting that exposure to high levels of dairy sludge could be detrimental to worms. However, the other study investigated the effects of long-term irrigation of fields with dairy sludge on earthworm populations and found that, while the non-irrigated site had a greater abundance of earthworms in fields not irrigated with dairy biosolids than those irrigated (303±51 verses 214±33; ~30% decrease), the mean individual biomass of earthworms was greater in irrigated pastures (0.85g verses 0.51g). Overall, it is not expected that the use of Organo-Sol as a diluted solution by broadcast application (25% solution) or spot-treatments (50% solution) in established lawns will have a considerable impact on earthworm populations.

Although no adverse effects to plants from lactic acid and citric acid were reported in the published literature, since Organo-Sol is considered to be a non-specific herbicide, it is expected that plants other than those listed specifically as target pests of Organo-Sol will be adversely affected in the event of direct contact. This has been demonstrated in efficacy field studies conducted with Organo-Sol where various grass species were affected. As a result a statement must be included on the label to advise users that temporary injury to turf may occur following application of Organo-Sol. Furthermore, greenhouse experiments were conducted to determine the sensitivity of non-target horticultural and floral species of plants. Suspensions of Organo-Sol at 25% and 50% applied alone, or in combination with the adjuvant Kornspec, and monitored for visible injury for one week. Cucumber, zucchini, bean, corn, pea, sugar beet, lettuce, carrot, marigold, cosmos, and pepper were tested. Organo-Sol at 25% concentration generated injury (up to 50% damage) on cucumber, zucchini, corn, and lettuce. Organo-Sol at 50% caused damage to cucumber, zucchini, corn, sugar beet, lettuce, carrot, peas, delphinium, and cosmos. Organo-Sol at either concentration did not cause damage to bean, eggplant, geranium, marigold and pepper. Based on the results from efficacy studies, precautionary measures must be included on the end-use product label to protect non-target horticultural plants and ornamentals.

Organo-Sol contains citric acid and lactic acid at 19.71 g/L and 17.69 g/L, respectively. The use of Organo-Sol will be limited to broadcast applications or spot-treatments on lawns, with no extended agricultural uses.

Given the ubiquitous nature of lactic acid and citric acid in animals, plants, edible food commodities and industrial chemicals, the proposed uses of Organo-Sol on lawns is not expected to result in a considerable increase in exposure to non-target terrestrial animals to citric and lactic acid. Furthermore, reports in published literature of cases of adverse effects from lactic acid and citric acid, as well as published toxicological endpoints for lactic acid and citric acid, do not suggest that that exposure of non-target terrestrial animals to the levels of lactic acid and citric acid in Organo-Sol will pose a concern with respect to toxicity. Given that lactic acid and citric acid are expected to undergo biotransformation and have very high mobility in soil, these acids are not expected to persist in the terrestrial environment. Based on these considerations exposure to lactic acid and citric acid from the use of Organo-Sol is not expected to result in an unacceptable risk to non-target terrestrial organisms.

Due to the low level of the MPCAs in Organo-Sol ($<7.0 \times 10^4$ CFU/g, combined), and that foreign lactic acid bacteria are not expected to persist in non-dairy environments, toxicity testing for effects on non-target soil microorganisms was not required. Furthermore, the use of Organo-Sol as a spot-treatment or broadcast application to control weeds in established lawns is not expected to affect environmentally or economically important microbial species or microbiologically-mediated biogeochemical processes.

4.2.2 Effects on Aquatic Organisms

Requests to waive testing on non-target aquatic organisms with lactic acid bacteria and lactic and citric acid were accepted based on the following information:

i) Effects on aquatic organisms from lactic acid bacteria:

Lactic acid bacteria are considered to be widespread but sporadic in the environment and can account for a small component of the natural microflora of healthy fish. *Lactobacillus* species have been isolated from saithe, Atlantic cod, Atlantic salmon (*Salmo salar* L.), rainbow trout (*Onchorhynchus mykiss*), wolfish (*Anarhichas lupus* L.) and Artic char (*Salvelinus alpinus*). In a Japanese study the relative percentage of lactic acid bacteria in fish among total bacterial levels ranged from 0.6–10% depending on the fish species, and lactic acid bacteria were present at 10^5–10^7 CFU/g. *Lactococcus lactis* was the predominant lactic acid bacteria species (99%) recovered from silver carp, common carp, channel catfish, and deep-bodied crucian carp in the summer months (June to October). The total concentration of lactic acid bacteria in the water was 10^4 CFU/mL during the same sampling time. A bacteriocin-producing *Lactococcus lactis* ssp. *lactis* isolate has also been recovered from farmed fish (turbot; *Psetta maxima*). The isolate demonstrated antimicrobial activity against *Listeria monocytogenes* and *Staphylococcus aureus*. *Lactococcus lactis* spp. *lactis* and *Lactococcus lactis* ssp. *cremoris* have also been recovered from smoked and sun-dried fish products.

A literature search conducted to determine whether there have been cases of infection in aquatic organisms from lactic acid bacteria in general, and from *Lactobacillus rhamnosus, Lactobacillus casei, Lactococcus lactis ssp. lactis* and *lactococcus lactis ssp. cremoris* specifically reported no adverse effects in freshwater fish, estuarine/marine fish, or aquatic plants.

Research has been conducted on the immune enhancement of fish and aquatic arthropods by probiotic lactic acid bacteria. Studies on the rainbow trout (*Onchorhynchus mykiss*) have been conducted using various probiotic strains (*Lactobacillus rhamnosus* strain ATCC 53103 and *Lactobacillus rhamnosus* strain JCM1136; *Lactococcus lactis* ssp. *lactis*) and dosing levels at approximately 10^5 to 10^{11} CFU/g of feed and exposure periods of 2 weeks to 30 days. No adverse effects were noted in the treated fish, and immune parameters of the fish were enhanced by the probiotic treatments. In a study on the use of probiotics in aquatic arthropods, brine shrimp (*Artemia nauplii*) were exposed to *Lactobacillus casei* strain CECT 4043 and *Lactococcus lactis* ssp. *lactis* strain CECT 539 in seawater at 1×10^8 bacteria/mL for 24 hours. No adverse effects from any of the lactic acid bacteria treatments were noted in *Artemia* cultures.

The lactic acid bacteria in Organo-Sol are present at a combined level of ~7.0×10^4 CFU/g, and the use of Organo-Sol is limited to broadcast applications or spot-treatments on lawns at 25–50% dilutions, with no direct application to aquatic systems. Given the lack of persistence of lactic acid bacteria in terrestrial non-dairy environments, and that the use of Organo-Sol is limited to established lawns, run-off into aquatic environments is expected to be minimal. Moreover, foreign lactic acid bacteria are not expected to persist in or on fish for more than a couple weeks, nor in aquatic systems for any prolonged period of time due to rapid biotransformation. Furthermore, a literature search revealed no reports of adverse effects in aquatic organisms from the species of lactic acid bacteria in Organo-Sol. Based on these considerations, exposure to lactic acid bacteria from the use of Organo-Sol is not expected to result in an unacceptable risk to non-target aquatic organisms.

ii) Effects on aquatic organisms from lactic acid and citric acid:

As previously mentioned, lactic acid and citric acid are naturally present in animals and humans, and in the environment in plants, including many edible commodities such as citrus and other fruit and vegetables. Lactic acid and citric acid are widely used in the food industry in various manufactured food products, such as in juices, beer and wine, candy and baked goods, and fermented dairy products. These acids are widely used in the chemical industry, including as inert ingredient in pesticides. Citric acid is on the U.S. EPA's *List of Inert Ingredients* as List 4A, whereas lactic acid is a List 4B inert ingredient.

A literature search conducted to determine whether there have been cases of adverse effects in aquatic organisms from citric acid and lactic acid revealed no reports of adverse effects to freshwater fish, estuarine/marine fish, aquatic arthropods, nor to aquatic plants from neither lactic acid nor citric acid.

Ecotoxicological values for lactic acid and citric acid in aquatic species were available in published literature.

Briefly, an ecotoxicological study was conducted with lactic acid, and some lactate esters, on various aquatic organisms, including two freshwater fish species (the zebra fish, *Brachydanio rerio*, and the fathead minnow, *Pimephales promelas*), the green microalga, *Selenastrum capricornatum*, and the crustacean, *Daphnia magna*. All tests were carried out using guidelines from the OECD and the U.S. EPA, and according to the OECD principles of Good Laboratory Practice. Briefly, in the 96-hour fish acute toxicity test with *B. rerio* and with *P. promelas*, fish were exposed to lactic acid at 10, 18, 32 or 56 mg/L under semi-static conditions. Both the 96-hour no observed effect concentration (NOEC) and the LC_{50} for fish were 320 mg/L. In the 72- and 96-hour growth inhibition tests with *S. capricornatum*, exponentially growing cultures of green algae (cell density: 10^4 cells/mL) were exposed to lactic acid at 10, 18, 32 or 56 mg/L and monitored for biomass, reproductive effects, and general signs of toxicity. The 72–96 hour NOEC for algae was 1900 mg/L, while the E_bC_{50} (biomass) was > 2800 mg/L and the E_rC_{50} was 3500 mg/L (reproduction based on cell count). In the 48-hour *Daphnia* sp. acute immobilization test with lactic acid at 10, 18, 32 or 56 mg/L (static conditions) the NOEC was 180 mg/L, while the EC_{50} was 240 mg/L.

The OECD reports that citric acid is of low toxicity to freshwater fish, daphnia, and algae with EC_{50} values ranging from approximately 100 mg/L to several hundreds of milligrams per litre. The LC_{50} values for fish range from 440–1516 mg/L. The only reported endpoint for a marine species, the crab, reports an LC_{50} of 160 mg/L. Tests that may qualify as sub-acute, or possibly long-term, show comparable endpoint values.

Organo-Sol contains citric acid and lactic acid at 19.71 g/L and 17.69 g/L, respectively, and the use of Organo-Sol is limited to broadcast applications or spot-treatments on lawns at 25–50% dilutions, with no direct application to aquatic systems. Lactic acid and citric acid are expected to undergo biotransformation in terrestrial environments but are also expected to redistribute into the aquatic environment based on their high mobility in soil. However, based on the levels of acids in Organo-Sol and that the use of the product is limited to established lawns, run-off and leaching into aquatic environments is expected to be minimal. In the aquatic environment, citric acid and lactic acid are expected to undergo rapid and complete biotransformation, and the potential for bioconcentration in aquatic organisms is low. Furthermore, reports in published literature of cases of adverse effects from lactic acid and citric acid, as well as published toxicological endpoints for lactic acid and citric acid do not show that exposure of non-target aquatic organisms to the levels of lactic acid and citric acid in Organo-Sol will pose a concern. Based on these considerations, exposure to lactic acid and citric acid from the use of Organo-Sol is not expected to result in an unacceptable risk to non-target aquatic organisms.

5.0 Value

5.1 Effectiveness Against Pests

Data including four controlled environment studies (i.e. conducted either in a greenhouse or in a growth chamber) and five field studies conducted over a three year period (2004-2006) at McGill University in Montreal, Quebec were submitted to demonstrate the efficacy of Organo-Sol applied with Kornspec Adjuvant, a representative of adjuvants which contain paraffin mineral oil at 83% and a blend of surfactants at 17%. Although experimental design, treatments, and environmental conditions were particular to each study, an appropriate scientific design was used and an appropriate set of treatments was included in these studies to evaluate the efficacy of the product for control of the target pests.

The level of clover control was assessed in all nine studies, while that for bird's-foot trefoil, black medic and wood sorrel was assessed in one, one, and two studies, respectively. In addition to the trial data, a scientific rationale was submitted in which it was argued that bird's-foot trefoil, black medic, and wood sorrel could be grouped together with clovers, based on taxonomy (i.e. they all belong to the *Rosidae* subclass and black medick, bird's-foot trefoil, and clovers also belong to the *Faboideae* subfamily) and leaf morphology (i.e. thin cuticle and small leaf size).

The efficacy of Organo-Sol applied with Kornspec Adjuvant was directly compared to that of Organo-Sol applied alone in three controlled environment studies.

The control of clover (70% white clover mixed with 30% red clover) following multiple applications of Organo-Sol plus Kornspec Adjuvant with a two, three, or four week spray interval was assessed in two field studies.

The efficacy of 25% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant was directly compared to that of 50% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant in four field studies.

The efficacy of Organo-Sol based treatments against the target pests, including clovers, bird's-foot trefoil, black medick, and wood sorrel in turf was visually assessed as percent control and compared to the untreated weedy check. Observations were made at various times throughout the growing season.

5.1.1 Acceptable Efficacy Claims

5.1.1.1 Red and White Clovers

The treatment of 25% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant resulted in an average of 41% control of clovers in the first week after treatment (13 data points over the 4 studies) and 49% control of clovers in the second week after treatment (18 data points over the 4 studies). In the one study in which a later evaluation was conducted, clovers had almost completely recovered in the third week after treatment (3 data points).

The treatment of 50% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant resulted in an average of 50% control of clovers in the first week after treatment (44 data points over 9 studies) and 55% control of clovers in the second week after treatment (21 data points over 4 studies). Recovery was evident in the third week after treatment in which control of clovers had declined to 18% (six data points over two studies).

Data from three controlled environment studies demonstrated that Organo-Sol required Kornspec Adjuvant at 3% v/v to achieve partial suppression of clovers. However, this adjuvant is no longer registered in Canada. Assist Oil Concentrate, XA Oil Concentrate and Kornoil Concentrate were supported as alternatives to Kornspec Adjuvant based on data generated from treatments of Organo-Sol plus Kornspec Adjuvant.

Since the herbicidal activity of Organo-Sol is short term, it would be expected that maximum performance requires multiple applications. Data from two field studies demonstrated that at least five applications made every two weeks are required to achieve an ongoing partial suppression of clovers.

As Organo-Sol contains living lactic acid bacteria, it would be expected that product efficacy may be reduced over time. Data from one field study demonstrated that the efficacy of Organo-Sol for clover control was reduced when the product was stored for two years or more.

5.1.1.2 Bird's-foot Trefoil, Black Medick, and Wood Sorrel

The efficacy of the treatment of 25% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant for control of bird's-foot trefoil, black medick, and wood sorrel was assessed in one field study each. Control was reported to be 28% for bird's-foot trefoil, 17% for black medic, and 15% for wood sorrel.

For the treatment of 50% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant, maximum control was observed to be 57% for bird's-foot trefoil (in one study), 65% for black medick (in one study) and 50% for wood sorrel (in two studies).

Partial suppression claims are supported based on the submitted data in combination with the following points:

- Bird's-foot trefoil, black medick, white clover and red clover all belong to the Faboideae subfamily of the Fabaceae family of the Fabales order. Wood sorrel is more distantly related, belonging to the Oxalidales order which belongs to the same subclass as the Fabales order;

- Leaves of plants belonging to the Fabales or Oxidales orders are typically delicate with thin cuticles thereby facilitating uptake of the herbicide; and

- The similarity in leaf size would be expected to result in a similar liquid retention capacity.

5.2 Phytotoxicity to Host Plant

The tolerance of turf to Organo-Sol, visually assessed as percent injury, was evaluated in seven efficacy studies, three of which were conducted under controlled environment conditions on a mixture of 30% Kentucky bluegrass, 40% creeping red fescue, and 30% perennial ryegrass and four of which were conducted in fields on a mixture of 90% Kentucky bluegrass and 10% red fescue. In one additional study, the tolerance of Kentucky bluegrass, perennial ryegrass, creeping bentgrass, creeping red fescue, chewings fescue and tall fescue to Organo-Sol was individually assessed.

Although experimental design, treatments, and environmental conditions were particular to each study, an appropriate experimental design was used and an appropriate set of treatments was included in each study to evaluate the tolerance to Organo-Sol treatments.

In six studies, the tolerance of turfgrass to a single application of Organo-Sol plus Kornspec Adjuvant was visually assessed as percent injury (%) at various times within three weeks after treatment.

In two field studies, the tolerance of turfgrass to multiple applications of Organo-Sol plus Kornspec Adjuvant with a two, three, or four week spray interval was visually assessed after each application.

5.2.1 Acceptable Claim for Host Plant

Injury to turf following a single application of 25% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant averaged 17% in the first week after treatment (14 data points over five studies), 6% in the second week after treatment (eight data points over five studies) and 8% in the third week after treatment (seven data points over four studies).

Injury to turf following a single application of 50% v/v Organo-Sol plus 3% v/v Kornspec Adjuvant averaged 33% in the first week after treatment (32 data points over seven studies), 10% in the second week after treatment (14 data points over seven studies) and 11% in the third week after treatment (10 data points over five studies).

It was demonstrated in the two multiple application studies that the level of injury sustained by turf following up to six applications of Organo-Sol with a two week spray interval was similar to that following a single application, indicating that turf recovered between applications.

Injury to turf grasses following application of Organo-Sol was typically lower than that sustained by target weeds, and turf recovered more quickly. However, a narrow margin of selectivity was evident. A statement was included on the label to advise that temporary injury to turf may occur (is likely) following application of Organo-Sol.

Organo-Sol may be an alternative to conventional chemical herbicides that are no longer available in some jurisdictions for cosmetic weed control in turf.

5.3 Impact on Succeeding Crops

Not applicable.

5.4 Economics

Not available.

5.5 Sustainability

5.5.1 Survey of Alternatives

5.5.1.1 Mechanical Control

Mechanical treatments include either removal of plant tissue above ground or removal of enough roots and crown to kill the weeds. Hand pulling before viable seeds form can effectively suppress or control some weed species. Manual removal of weeds from turfgrass, although time-consuming, is feasible on small individual properties.

5.5.1.2 Healthy Lawn Management

A healthy lawn can effectively compete with weeds thereby suppressing weed growth. Good turf management practices include adequate fertility, proper mowing height, overseeding and top dressing when necessary, liming when soil is too acidic, aeration, and proper irrigation (watering when required).

5.5.1.3 Chemical Control Practices

In large turf areas such as parks, athletic fields, and golf courses or when weed infestations are heavy, it is not practical to manually remove weeds. Chemical weed control has been the common practice if weed infestations become unmanageable.

Applications of conventional herbicides (alone or in a tank mixture), including Groups four, two and six herbicides, may be periodically required for control of broadleaf weeds in turf (Table 5.5.1-1).

Table 5.5.1-1. Alternative herbicides for control of clovers, bird's-foot trefoil, and black medick in turf

TGAI	End-use Products	Pest Claims Including	Herbicide Classification	
			Group	Mode of Action
MCPA	Compitox L	Clovers and black medick	4	Synthetic auxin
Mecoprop-P	MCPP-p 600 L	Clovers and black medick	4	Synthetic auxin
Dicamba	Oracle	Clovers	4	Synthetic auxin
2,4-D + mecoprop	Wilson Turf-Rite	Clovers and black medick	4	Synthetic auxin
Clopyralid	Transline	Clovers	4	Synthetic auxin
2,4-D + mecoprop + dicamba	Killex 500	Clovers, bird's-foot trefoil, and black medick	4	Synthetic auxin
Chlorsulfuron	Telar	Clover and bird's-foot trefoil	2	ALS inhibitor
Bentazon	Basagran	Clovers	6	Inhibition of photosynthesis

No herbicides are presently registered for control of wood sorrel in turf.

The availability of Organo-Sol will provide both homeowners and commercial applicators with another option for control of clovers, black medick, and bird's-foot trefoil in situations where the use of synthetic chemicals is not desirable and a new option for control of wood sorrel on turf.

5.5.2 Compatibility with Current Management Practices Including Integrated Pest Management

Organo-Sol, an alternative to conventional turf herbicides, could be used as a component of a sustainable integrated pest management program in turf.

5.5.3 Information on the Occurrence or Possible Occurrence of the Development of Resistance

Based on the mode of action of Organo-Sol, the development of resistance is unlikely. Development of resistance of clovers, bird's-foot trefoil, black medick, and wood sorrel to chemical herbicides has not been found in Canada. However, the availability of an alternative tool like Organo-Sol may reduce the potential for the development of weed resistance to chemical herbicides.

5.5.4 Contribution to Risk Reduction and Sustainability

Organo-Sol herbicide would be a viable component of sustainable integrated pest management program in turf.

6.0 Pest Control Product Policy Considerations

6.1 Toxic Substances Management Policy Considerations

The management of toxic substances is guided by the federal government's Toxic Substances Management Policy (TSMP), which puts forward a preventive and precautionary approach to deal with substances that enter the environment and could harm the environment or human health. The policy provides decision makers with direction and sets out a science-based management framework to ensure that federal programs are consistent with its objectives. One of the key management objectives is virtual elimination from the environment of toxic substances that result predominantly from human activity and that are persistent and bioaccumulative. These substances are referred to in the policy as Track 1 substances.

In its review, the PMRA took into account the federal Toxic Substances Management Policy and followed its Regulatory Directive DIR99-03, The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy. Technical microbial pest control agents can not be compared against the TSMP criteria as the science on which the criteria were developed is based on the behaviour of chemical substances. As this product consists of an organism (bacteria) and chemicals produced by the organism, under TSMP PMRA considered pesticidally active chemicals produced and substances associated with the product (i.e. formulants and microcontaminants) , but not the biological organisms. Consideration under TSMP also includes microcontaminants in the technical products, *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, and *Lactococcus lactis* ssp. *cremoris* Technical, and formulants in the manufacturing concentrate and end-use product, DOM Manufacturing Concentrate and Organo-Sol respectively. The PMRA has reached the following conclusions:

- The chemicals identified as having pesticidal activity are citric and lactic acid. Lactic acid and citric acid are naturally present in animals and humans, and in the environment in plants, including many edible commodities such as citrus and other fruit and vegetables. Lactic acid and citric acid are widely used in the food industry in various manufactured food products. Persistence and potential bioconcentration are expected to be low. Based on these considerations, TSMP Track 1 criteria are not met.

- There are no formulants, contaminants or impurities present in the manufacturing concentrate or end-use product that would meet the TSMP Track 1 criteria. Therefore, the use of Organo-Sol and DOM Manufacturing Concentrate are not expected to result in the entry of Track 1 substances into the environment.

7.0 Summary

7.1 Methods for Analysis of the Micro-organism as Manufactured

The product characterization data for *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate and Organo-Sol were judged to be adequate to assess their potential human health and environmental risks. The technicals and manufacturing concentrate were characterized and the specifications of the end-use product were supported by the analyses of a sufficient number of batches. Since there was no method submitted for strain-specific identification of the five microbial pest control agents, the registrant will be required to address this data requirement.

7.2 Human Health and Safety

The human health and safety information and data submitted in support of citric acid, lactic acid, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, *Lactobacillus rhamnosus* strain LPT-21, and *Lactobacillus casei* strain LPT-111 were determined to be sufficiently complete to permit a decision on registration.

At the concentrations present in Organo-Sol, the lactic acid bacteria used in the manufacture of Organo-Sol are not expected to pose a significant risk via the oral route of exposure. Literature searches did not yield reports of dermal toxicity or irritation associated with the lactic acid bacteria used in the manufacture of Organo-Sol. Similarly, eye irritation was not reported for the *Lactobacillus* species. No cases of eye irritation or infection could be definitively linked to *Lactococcus* species.

The fermentation products, citric acid and lactic acid, are of low acute toxicity by the oral route. Lactic acid is of low acute toxicity via the dermal route while both lactic and citric acid are slightly irritating to the skin. Eye irritation studies indicated that, at the concentrations found in Organo-Sol, lactic acid and citric acid are capable of producing moderate to severe injury to the eye, particularly with repeated or prolonged exposure.

Lactic acid was not found to be a dermal sensitizer. Although no hypersensitivity studies were available on the lactic acid bacteria used in the manufacture of Organo-Sol or citric acid, their levels in the technicals and/or end-use products along with their extensive history of use in food production indicate that there is minimal risk of sensitization. The Organo-Sol end-use product, however, may contain unmodified milk protein which is considered an allergen.

Occupational exposure to the lactic acid bacteria used in the manufacture of Organo-Sol, citric acid and lactic acid are expected to be minimal from the proposed use pattern if the recommended personal protective equipment and re-entry precaution statements on the product label are observed.

There is a potential for non-occupational exposure to adults, infants and children as the label does allow applications to residential and public areas. The associated risk, however, is expected to be low based on the low acute toxicity/pathogenicity profile for the lactic acid bacteria species, citric acid and lactic acid in Organo-Sol.

As there are no food uses proposed for Organo-Sol, dietary exposure to the lactic acid bacteria, citric acid and lactic acid is expected to be negligible to non-existent.

7.3 Environmental Risk

The scientific rationales and published scientific literature submitted in support of *Lactobacillus rhamnosus* Technical, *Lactobacillus casei* Technical, *Lactococcus lactis* ssp. *lactis* Technical, *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate, and Organo-sol were determined to be sufficiently complete to permit a decision on registration.

Waiver rationales were submitted to address the hazards of citric acid, lactic acid, *Lactobacillus* casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL to non-target organisms. These rationales and other published information showed that the use of Organo-sol does not pose a risk to birds, mammals, arthropods (including honeybees), fish, non-arthropod invertebrates, plants, or algae.

No additional studies were required to address the environmental fate and behaviour of citric acid, lactic acid, *Lactobacillus* casei strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strains LL64/CSL and LL102/CSL, and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL. Environmental fate data (Tier II/III) are not normally required in the absence of toxicological effects in non-target organisms in Tier I testing.

As a precaution, standard label statements will prohibit handlers from contaminating aquatic habitats.

7.4 Value

The data submitted supported a partial suppression claim for white clover, red clover, bird's-foot trefoil, black medick, and wood sorrel. Organo-Sol offers an alternative to the use of chemical herbicides for weed management in turf.

8.0 Proposed Regulatory Decision

Health Canada's PMRA, under the authority of the *Pest Control Products Act* and Regulations, is proposing full registration for the sale and use of *Lactobacillus casei* Technical, *Lactobacillus rhamnosus* Technical, *Lactococcus lactis* ssp. *lactis* Technical and *Lactococcus lactis* ssp. *cremoris* Technical, DOM Manufacturing Concentrate and the end-use product Organo-Sol, containing the microbial pest control agents *Lactobacillus casei* strain LPT-111, *Lactobacillus rhamnosus* strain LPT-21, *Lactococcus lactis* ssp. *lactis* strain LL64/CSL, *Lactococcus lactis* ssp. *lactis* strain LL102/CSL and *Lactococcus lactis* ssp. *cremoris* strain M11/CSL, for the partial suppression of clovers, black medick, bird's-foot trefoil, and wood sorrel in established lawns.

An evaluation of available scientific information found that, under the approved conditions of use, the product has value and does not present an unacceptable risk to human health or the environment.

List of Abbreviations

µg	micrograms
ADI	acceptable daily intake
ARD	acute reference dose
atm	atmosphere
BOD	biological oxygen demand
bw	body weight
°C	degree(s) Celsius
CAS	Chemical Abstracts Service
CFU	colony forming unit
COD	chemical oxygen demand
cm^2	centimetre squared
DOC	dissolved oxygen content
DNA	deoxyribonucleic acid
EC_{50}	effective concentration on 50% of the population
g	gram
Hg	mercury
IUPAC	International Union of Pure and Applied Chemistry
kg	kilogram
K_{oc}	organic-carbon partition coefficient
L	litre
LC_{50}	lethal concentration 50%
LD_{50}	lethal dose 50%
m	metre
m^2	metre squared
m^3	metre cubed
MA	manufacturing concentrate
mg	milligram
mL	millilitre
mm	millimetre
NOEC	no observed effect concentration
OECD	Organisation for Economic Co-operation and Development
p*K*a	dissociation constant
PMRA	Pest Management Regulatory Agency
RAPD-PCR	random amplification of polymorphic DNA – polymerase chain reaction
$t_{1/2}$	half-life
TGAI	technical grade active ingredient
TSMP	Toxic Substances Management Policy
USEPA	United States Environmental Protection Agency
v/v	volume per volume dilution

Appendix I Tables and Figures

Table 1 Toxicity to Non-Target Species (*Lb. rhamnosus* strain R-11, *Lb. casei* strain 215 , *Lc. lactis* ssp. *lactis*, and *Lc. lactis* ssp. *cremoris*)

Organism	Exposure	Test Substance(s)	Effects/Comments	Reference(s)
Terrestrial Organisms				
			Vertebrates/Ivertebrates/Plants	
Birds (Bobwhite Quail) Terrestrial arthropods Terrestrial Plants Non-arthropod Invertebrates			Waiver requests were submitted stating that the increase in environmental exposure to LAB from the use of Organo-Sol will be minimal; the LAB and all raw materials in Organo-Sol are food-grade ingredients commonly used for the manufacturing of food for humans and animals; the results from a published literature search indicated few reports of adverse effects to wild birds, terrestrial arthropods, plants, and that while high levels of dairy sludge may be detrimental to earthworms, adverse effects are not expected given the proposed use pattern; and there is a history of use of LAB as probiotics in animals, particularly chickens. However, as the end-use product is a non-specific herbicide, plants other than those listed specifically as target pests will be adversely affected in the event of direct contact. **WAIVER ACCEPTED**	PMRA 1627043 PMRA 1627092 PMRA 1627098 PMRA 1627101
Wild Mammals			No study or waiver was submitted. However, since the increase in environmental exposure to the LAB from the use of Organo-Sol will be minimal; the LAB and all raw materials in Organo-Sol are food-grade ingredients commonly used in the food industry for the manufacturing of food for humans and animals; the results from a published literature search indicating no reports of adverse effects in wild mammals, and that LAB are relatively rare cause of clinical infections in humans, particularly given their ubiquity, the requirement for non-target testing on wild mammals was waived. Furthermore, literature indicated a history of use of LAB for health promoting effects in humans, with few cases of infections.	n/a
Soil microbes			No study or waiver submitted. Effects data are not required since *Lb. rhamnosus*, *Lb. casei*, *Lc. lactis* ssp. *lactis* and *Lc. lactis* ssp. *cremoris* are normal components of the soil, and the organisms are not expected to affect environmentally or economically important microbial species or microbiologically mediated biogeochemical processes.	n/a

Organism	Exposure	Test Substance(s)	Effects/Comments	Reference(s)
Aquatic Organisms				
			Vertebrates/Invertebrates/Plants	
Freshwater Fish Estuarine/Marine fish Aquatic Arthropods Aquatic Plants	Waiver requests were submitted stating that the increase in aquatic exposure to the LAB in Organo-Sol from on the proposed use pattern will be minimal; and the results from a published literature search for reports of adverse effects to aquatic organisms, toxicological endpoints of LAB in aquatic organisms, and a history of use of LAB for health promoting effects in fish yielded no results. Furthermore, the published literature shows a lack of persistence of LAB in aquatic organisms and aquatic environments. **WAIVER ACCEPTED**			PMRA 1627086 PMRA 1627095 PMRA 1627101

Table 2 Toxicity to Non-Target Species (lactic acid and citric acid)

Organism	Exposure	Test Substance(s)	Effects/Comments	Reference(s)
Terrestrial Organisms				
			Vertebrates/Invertebrates/Plants	
Birds (Bobwhite Quail) Terrestrial Arthropods Non-arthropod Invertebrates Terrestrial Plants	Waiver requests were submitted stating that the increase in environmental exposure to lactic acid and citric acid from the use of Organo-Sol will be minimal; lactic and citric acid are commonly used in the food and chemistry industry; and there is history of use of lactic acid and citric acid in animal feed, particularly chicken feed. Furthermore, the results from a published literature search showing no reports of adverse effects to wild birds; terrestrial plants; direct exposure to arthropods may result in some degree of toxicity to arthropods, however, adverse effects are not expected given the proposed use pattern; high levels of lactic acid and citric acid dairy sludge may be detrimental to earthworms, however, adverse effects are not expected given the proposed use pattern. **WAIVER ACCEPTED**			PMRA 1627043 PMRA 1627092 PMRA 1627098 PMRA 1627101
Wild Mammals	No study or waiver was submitted. Based on the fact that the increase in environmental exposure to lactic acid and citric acid from the use of Organo-Sol will be minimal; lactic and citric acid are commonly used in the food and chemistry industry; and the results from a published literature search indicating no reports of adverse effects in wild mammals, the requirement for non-target testing on wild mammals was waived.			n/a
Soil microbes	No study or waiver required.			n/a

Organism	Exposure	Test Substance(s)	Effects/Comments	Reference(s)
Aquatic Organisms				
Vertebrates/Invertebrates/Plants				
Freshwater Fish Estuarine/Marine fish Aquatic Arthropods Aquatic Plants	A waiver request was submitted based on the fact that the increase in environmental exposure to lactic acid and citric acid from the use of Organo-Sol will be minimal and the lack of persistence of lactic acid and citric acid in aquatic organisms and aquatic environments. **WAIVER ACCEPTED**			PMRA 1627086 PMRA 1627095 PMRA 1627101

References

A. List of Studies/Information Submitted by Registrant

1.0 Applicant Submitted Data - Unpublished Information

PMRA Document Number: 1626955
Reference: 2007, Codex alimentarius commission, Codex stan 192-1995, FAO & WHO. FAO Headquarters, Rome, Italy, Data Numbering Code: M1.3,M2.9.3,M4.0,M9.0

PMRA Document Number: 1626956
Reference: 2008, Confirmation of organic acid composition of Organo-sol and the absence of formic acid in Organo-Sol, Data Numbering Code: M10.0

PMRA Document Number: 1626957
Reference: 2005, Dose-response experiment in greenhouse, Data Numbering Code: M10.0

PMRA Document Number: 1626958
Reference: 2006, Weed suppressive activity of Organo-sol, dairy by-product, Data Numbering Code: M10.0,M2.7.2

PMRA Document Number: 1626959
Reference: 2005, Weed suppressive activity of Organo-sol, dairy by-product, Data Numbering Code: M10.0,M9.8.1

PMRA Document Number: 1626960
Reference: 2006, Weed suppressive activity of Organo-sol, dairy by-product, Data Numbering Code: M10.0,M9.8.1

PMRA Document Number: 1626962
Reference: 2007, Product characterization and analysis, Data Numbering Code: M2.0 Confidential Business Information

PMRA Document Number: 1626968
Reference: Institut Rosell, Lactobacillus casei Rosell-215, Data Numbering Code: M2.7.2

PMRA Document Number: 1626969
Reference: Institut Rosell, Lactobacillus rhamnosusi Rosell-011, Data Numbering Code: M2.7.2

PMRA Document Number: 1626975
Reference: 2002, DOM, a mix containing Lactococcus lactis subsp. lactis and Lactococcus lactis subsp. cremoris, Data Numbering Code: M2.7.2,M2.8

PMRA Document Number: 1626976
Reference: 2007, Guides des bonnes pratiques industrielles (BPI), Data Numbering Code: M2.8

PMRA Document Number: 1626977
Reference: 2007, Certificate of registration, Data Numbering Code: M2.8

PMRA Document Number: 1626978
Reference: 2002, Certificate of analysis, Data Numbering Code: M2.8

PMRA Document Number: 1626979
Reference: 2008, Organo-Sol Manufacturing and Quality Assurance Processes, Data Numbering Code: M2.8 Confidential Business Information

PMRA Document Number: 1626981
Reference: 2007, Whey analysis, Data Numbering Code: M2.8

PMRA Document Number: 1626982
Reference: 2008, Organo-Sol Analysis (5 batches), Data Numbering Code: M2.10.1,M2.10.2,M2.8 Confidential Business Information

PMRA Document Number: 1626983
Reference: 2007, Certificat d analyse, Data Numbering Code: M2.10.2,M2.8 Confidential Business Information

PMRA Document Number: 1626984
Reference: 2005, Sucres et acides organiques avec HPLC Dionex, Data Numbering Code: M2.10.1,M2.12,M2.8,M2.9.2,M2.9.3

PMRA Document Number: 1626988
Reference: 2007, Summary, human health and safety testing, Data Numbering Code: M4.1

PMRA Document Number: 1626989
Reference: 1992, Citric acid, Data Numbering Code: M4.1,M9.1

PMRA Document Number: 1626991
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B. Additional Information Considered - Published Information

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1766385 CCOHS Chemical Name: Lactic Acid , DACO: 2.7,9.3,9.4,9.5,9.6,9.7,9.8,M9.2

1766386 RTECS Lactic acid, DACO: 2.7,9.3,9.4,9.5,9.6,9.7,9.8,M9.2

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